UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

006021

JUL 9 1990

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Difethialone

Project No.: 0-1068
TOX Chem No.: 114AAB

FROM: Ray Landolt 6/29/90
Review Section I
Toxicology Branch II - Herbicide, Fungicide, and
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Health Effects Division (H7509C)

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THRU: Mike Ioannou, Section Head
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and
Marcia van Gemert, Branch Chief
Toxicology Branch II - Herbicide, Fungicide, and
Antimicrobial Support
Health Effects Division (H7509C) 7/6/90

Registrant: LiphaTech, Letter of April 3, 1990

Action Requested: Review an Acute Oral Toxicity Study in the beagle dog (MRID 414422-01) submitted in support of dose levels to be administered in the proposed dog antidotal treatment study.

Conclusion: Classification of Data: Minimum

Estimated oral LD_{50} in the beagle dog is 11.81 (6.60-21.16) mg/kg.

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Reviewed By: Ray Landolt 6/29/90
Section I, Toxicology Branch - HFAS (H7509C)
Secondary Reviewer: Mike Ioannou, Section Head 7/3/90
Section I, Toxicology Branch - HFAS (H7509C)

DATA EVALUATION REPORT

Study Type: Acute Oral Toxicity -Dog

Project No.: 0-1068

Test Material: Difethialone
(anticoagulant rodenticide)

TOX Chem No.: 114AAB

MRID No.: 414422-01

Synonyms: LM-2219

Study Date: June, 1985

Study Number: 84.08 LM-2219 Cpp
84.11 LM-2219 Cpp

Sponsor: Chempar

Testing Facility: Lipha Research Center
Lyon, France

Title of Report: LD_{50} Evaluation of LM-2219 Given Orally to Beagles

Author: Ch. Mally and Porret-Blanc

Conclusions:

Core Classification - Minimum

Estimated LD_{50} = 11.81 (6.60-21.16) mg/kg

This study is not a Toxicity Guideline Requirement.

However, it does contain valuable information on the acute toxicity of difethialone in the beagle dog.

The lack of a sufficient number of animals at the high and low dose levels should not detract from it's use as an acceptable study.

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A. Material:

Test Material LM-2219, lot JCM 1075 with a purity of 89.36% was used in this study.

Beagle dogs- 10 males (10.8-16 Kg) and 9 females (10-12.1 Kg)

B. Study Design:

The test material (LM-2219) was administered orally in capsules(000) without a vehicle at the following levels:

Dose (mg/kg)	No. of Animals	
	Males	Females
100	1	
20	6	6
10	2	1
5	1	2

All animals were observed twice daily for 21-35 days. Body weights were recorded prior to treatment, then weekly thereafter.

Coagulation parameters were determined from blood samples taken prior to treatment, daily from days 3-14, then on days 18, 21, 25, 28, and 35. Plasma prothrombin time in seconds was determined by the Quick one-stage method. Prothrombin activity reported as percent of normal was determined from the dilution curve of the relationship of prothrombin concentration to clotting time of the plasma obtained from eight nontreated dogs.

Necropsy was preformed on all animals found dead and surviving the 21-35 day observation period. Tissue for histopathological examination was taken from liver and kidney.

"The calculation of the LD_{50} was preformed by the method of Litchfield and Wilcoxon, taking into account the unequal number of animals. The confidence limits were determined according to Litchfield and Wilcoxon (1949)."

C. Results:

LD_{50} was estimated to be 11.81 mg/kg, with 95% confidence limits of 6.6 to 21.16 mg/kg.

At the 5.0 mg/kg level, no clinical signs of toxicity, a stable body weight gain, and no deaths were reported. Slight changes in prothrombin times (sec.) and activity (%) were reported at this level. Prothrombin time was prolonged from 7-8 seconds prior to treatment, to 8-9 seconds during days 4-14 being comparable to the control values by day 21. Prothrombin activity decreased from 85-100% prior to treatment to 50-85% during days 3-14 being comparable to the control values by day 21.

At the 20 mg/kg level, of the 9/12 deaths reported, 7 animals died during the 7-10 day observation period. Two animals died on days 15 and 18, repectively. Prior to death, during days 7-10, these animals exhibited pale mucous membranes, appeared weak with increased respiration. Hematomas of the extremities and in the area of the veinous puncture were observed. Death was related to pulmonary hemorrhage.

Body weight of the animals to survive the observation period remained comparable to the pretest values.

A prothrombin time control value of 7 seconds was prolonged by 12-26 seconds by day 3, 38-123 seconds by day 7 and returning to control values (7-9 sec.) by day 28 (for those animals surviving the 35 day observation period).

A prothrombin activity control value of 100% decreased to 22-33% by day 3, 5-10% by day 7 and were in the range of 50-100% by day 28 (for those animals surviving the 35 day observation period).

Necropsy of those animals that died during the study showed hemorrhage in the abdominal and thoracic cavities with the thymus cited as the target organ.

Histopathological examination of those animals that died during the study "revealed an extra medullary hematopoiesis, hepatic and splenic compensation for the loss of figurative blood elements and an hepatocellular and Kupfferian pigmentation originating from the hemoglobin catabolism." (French to English Tranalation)

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END